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INVITED EDITORIAL
Gene Regulation by mRNA Editing

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The commonly cited figure of 10^5 genes in the human genome represents a tremendous underestimate of our capacity to generate distinct gene products with unique functions. Our cells possess an impressive collection of tools for altering the products of a single gene to create a variety of proteins. The different gene products may have related but distinct functions, allowing cells of different types or at different developmental stages to fine-tune their patterns of gene expression. These tools may act in the cytoplasm, as when proteins undergo post-translational modifications, or in the nucleus, in the processing of pre-mRNA.

Two forms of intranuclear fine-tuning are well established and widely studied: alternative splicing of pre-mRNAs and alternative polyadenylation site selection. In recent years it has become clear that cells possess yet another tool to create RNA sequence diversity, mRNA editing. The term "editing" is applied to posttranscriptional modifications of a purine or pyrimidine, which alter an mRNA sequence as it is read, for example, by ribosomes. Covalent changes to the structure of nucleotide bases are well known to occur on tRNA and rRNA molecules, but such changes in mRNA sequence are novel in that they have the capacity to change specific protein sequences.

Despite the potential power of mRNA editing to generate new and useful gene products, it is clear that, like splicing and polyadenylation, it must be tightly regulated. Unrestricted mRNA processing could lead the cell to synthesize toxic proteins or to make an otherwise useful protein at the wrong time. The control of these functions is only beginning to be understood, but there are fascinating hints that the different classes of intranuclear pre-mRNA processing are coordinated. As our understanding of these events matures, we may come to see them each as different aspects of a single RNA-processing mechanism.

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Forms of mRNA Editing

To date, four classes of mRNA editing have been observed in mammalian cells (fig. 1); it seems unlikely that this list is complete. Because it has not been possible to search systematically for discrepancies between mRNA and genomic sequences, the list of mRNAs known to be edited is short, but it will almost certainly expand as this novel aspect of gene regulation is explored.

C-to-U Editing and the ApoB mRNAs

The first recognized and best-understood example of editing in mammalian cells occurs in epithelial cells of the small intestine, enterocytes. These cells synthesize a form of apolipoprotein B, ApoB-48, and insert it into chylomicrons, the carrier particles that allow dietary lipid to circulate in the bloodstream. Human liver cells express the identical gene, *ApoB,* but they synthesize the larger protein, ApoB-100, found in another class of lipid carrier, the LDL particle. ApoB-48 and ApoB-100 peptide sequences are identical at their N-termini, but ApoB-48 terminates at 48% of the length of the longer protein. A single base difference accounts for a break in the open reading frame in the ApoB-48 mRNA. Nucleotide 6666 in ApoB-100 is the C in the glutamine codon CAA; the corresponding nucleotide in ApoB-48 is a U, forming the stop codon UAA. This UAA is not encoded in any genomic copy of *ApoB.* As first suggested nearly a decade ago, U6666 is the product of a covalent change in ApoB mRNA sequence (Chen et al. 1987; Powell et al. 1987; Higuchi et al. 1988).

Boström et al. (1990) developed an in vitro mRNA-editing assay and demonstrated that the C-to-U modification involves the direct deamination of cytosine to form uracil (fig. 1), and they found this enzymatic activity in lysates from a variety of cells, including several that do not express the *ApoB* gene. The sequence specificity of editing is directed by an 11-nucleotide sequence (described as the mooring sequence) located 5 nucleotides 3′ of a cytosine; this sequence is sufficient to allow some heterologous mRNA species to be edited. The efficiency of editing also depends on other *cis*-regulatory

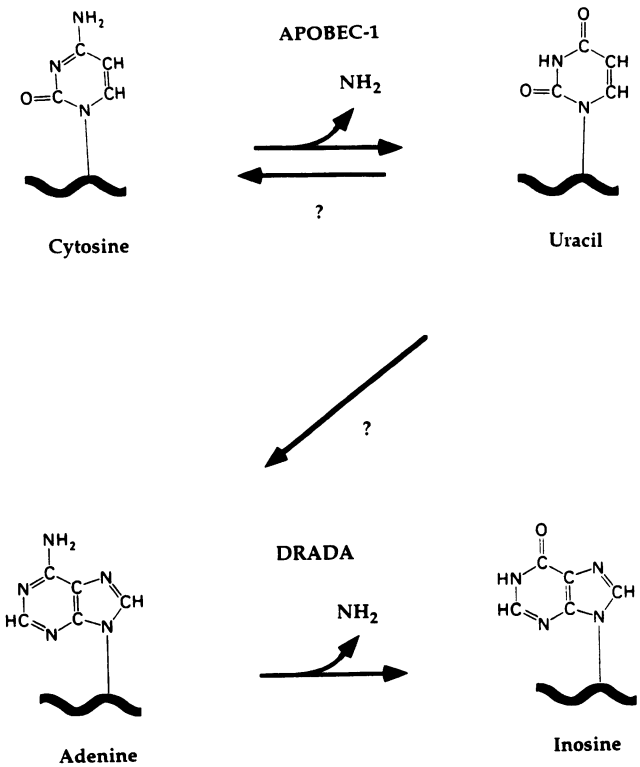

Figure 1 Four known classes of mRNA editing. The deamination of cytosine to form uracil is peformed by the enzyme APOBEC-1. The deamination of adenine to form inosine is performed by DRADA. The mechanisms are not known for the other two classes of editing, conversion of a uracil to a cytosine or to an adenine. These reactions may involve base substitution rather than covalent modification. For details, see the text.

sequence features, including sequence 5′ to the edited C, as well as the A/T richness of the RNA near the site (Driscoll et al. 1993; Backus and Smith 1994).

The enzymatic machinery that performs cytosine deamination is still only partially characterized. The ApoB-editing catalytic subunit (APOBEC-1) has been cloned from several mammalian species (Hadjiagapiou et al. 1994; Osuga et al. 1995). APOBEC-1 is generally the limiting factor for editing of ApoB mRNA. The only human tissue where APOBEC-1 is expressed in the adult is the small intestine (where ApoB-48 is made), but in rodents and several other mammals APOBEC-1 is expressed in both the small intestine and the liver (Greeve et al. 1993), and in these species the liver synthesizes both ApoB-48 and ApoB-100 (Patterson et al. 1992). Giannoni et al. (1995) report that the human fetal small intestine acquires the ability to edit apoB mRNA as APOBEC-1 accumulates in that tissue. The APOBEC-1 protein is localized to the nucleus of most enterocytes, but some histological sections show cytoplasmic staining as well. However, ApoB mRNA editing is a strictly nuclear process (Lau et al. 1991), occurring after polyadenylation is complete and while the pre-mRNA is undergoing splicing. Lau et al. (1991) found that some but not all of the edited ApoB pre-mRNA had already spliced out one of the adjacent introns, suggesting that the processing pathway has some flexibility. It is interesting to speculate that the order of these events could be significant. Nonsense-mediated decay of nuclear RNAs appears to occur only in transcripts with introns (Maquat 1996). Editing after splicing is complete could allow for stable expression of mRNAs that encode truncated proteins.

APOBEC-1 is homologous to other cytosine deaminases and, like them, has a critical zinc ion complexed at its active site (Yamanaka et al. 1994; MacGinnitie et al. 1995). In its purified state, this enzyme is inactive, but when supplemented with cell extract—even taken from many cell types or organisms that do not edit the ApoB mRNA—it supports editing in vitro (Teng and Davidson 1992). The necessary cofactors appear to have other conserved functions, possibly in nuclear RNA processing. APOBEC-1 binds RNA weakly and with little specificity, but in the presence of cofactors it associates specifically with target mRNA sequences (Anant et al. 1995*a*, 1995*b*). Two proteins, defined only as p44 and p66, can be cross-linked to the mooring sequence and are believed to participate in editing (Lau et al. 1991). Yang and colleagues (Yang and Smith 1996) have purified APOBEC-1 and have conjugated it to beads, to enrich for editing-related proteins in cellular extracts. Proteins eluted from these beads are found to support editing. Although the number of proteins in this eluant is still daunting, this and other complementary approaches (Harris et al. 1993; Schock et al. 1996) should allow biochemists for the first time to reconstitute the editing reaction with fully defined components.

In parallel with these biochemical studies, the *Apobec-1* gene has been manipulated in vivo. Several surprises have emerged from studies in which this gene either was overexpressed in cells or whole animals or was ablated by gene targeting. Rat liver cells that overexpress APOBEC-1 edit the usual site in endogenous ApoB mRNA, with three- to sixfold greater efficiency, but edit downstream C nucleotides at higher-than-normal levels (Sowden et al. 1996). This "hyperediting" is relatively nonspecific in its sequence requirements, but, as with normal editing, it is completely dependent on cofactors to target and activate the enzyme. Furthermore, the presence of a canonical mooring sequence is not sufficient to mark an mRNA either for normal editing or for hyperediting. On the basis of these results, Yamanaka et al. (1996) suggest that the targeting of the editing machinery occurs in two steps. First, cofactor proteins, recognizing some sequence feature distinct from the mooring sequence, bind to the target RNA. Second, the editing complex, including APOBEC-1, becomes anchored to a

specific site through the mooring sequence. In hyperediting, the process remains dependent on the first step, but the requirement for the second is relaxed.

Yamanaka et al. (1995) generated transgenic animals—both mice and rabbits—that overexpress APOBEC-1 in their livers. Such animals exhibit both high-efficiency normal editing and hyperediting (Yamanaka et al. 1996). They do not express ApoB-100, and hence their lipoprotein profile is abnormal. Transgenic animals of both species have abnormal liver morphology, with fibrosis and dramatic accumulation of intracellular lipid droplets. Among the mice, four independent transgenic lines showed a similar dysplasia, and in each line some animals also developed hepatic carcinomas. Yamanaka et al. suggest that promiscuous editing of regulators of the cell cycle could explain these results. One mRNA that they examined, which encodes the TEC tyrosine kinase, contains a mooring sequence and is indeed edited at a low level in transgenic but not in control animals. These data show that, in principle, an editing enzyme can act as an oncogene, a point that will be discussed below.

Mice in which APOBEC-1 expression is abolished by gene targeting display a surprisingly mild phenotype. They synthesize chylomicrons, which are cleared from the plasma with normal kinetics, despite the complete absence of ApoB-48. They appear to have unusually high levels of LDL. These animals are completely lacking in ApoB mRNA editing, and they synthesize ApoB only in the ApoB-100 form, demonstrating that there is no redundant system for terminating the ApoB mRNA open reading frame. This result is somewhat unexpected, because of the results of Yao et al. (1992) and Heinemann et al. (1994). These groups have shown premature polyadenylation of ApoB mRNA sequence variants that could not be edited and of variants where editing does not introduce a termination codon. The polyadenylation of each of these mRNA species occurred at cryptic sites close to the usual editing site. The ApoB protein made from these mRNAs could not be distinguished in size from ApoB-48. These results are intriguing because they suggest that the mechanisms for mRNA editing and for polyadenylation (like those for splicing and polyadenylation; see Niwa and Berget 1991) are coupled.

Beyond ApoB

The phenotypic analysis of APOBEC-$1^{-/-}$ mice demonstrates two points. First, mice have no parallel pathway to edit apoB mRNA in the absence of APOBEC-1. Second, even if APOBEC-1 has other target mRNAs in normal mice, there is no obvious consequence to an animal if this interaction does not occur. This may be because APOBEC-1 is absolutely specific, or because other editing enzymes can perform a similar function. The work of Skuse et al. (1996) suggests that, indeed, the APOBEC-1 cytosine deaminase activity is not unique. This group has shown that human NF1 mRNA, which has a near-canonical mooring sequence, undergoes a C-to-U modification at a site predicted to truncate the open reading frame and to change a CGA arginine codon to a UGA termination codon. NF1 mRNA editing appears to be analogous to the editing of ApoB mRNA, but, although Skuse et al. confirm that APOBEC-1 is limiting for the efficient editing of ApoB mRNA in transfected cell lines, they find no evidence that NF1 mRNA editing is enhanced by coexppression of APOBEC-1. Although this may simply indicate that some other factor is limiting for efficient editing of NF1, it is also possible, as Skuse et al. suggest, that different catalytic subunits are used to edit distinct mRNA species. This is a critical point that should be revisited by testing for NF1 mRNA editing in cells from APOBEC-1–deficient mice. If NF1 editing proceeds normally in the absence of this enzyme, the APOBEC-$1^{-/-}$ phenotype will have to be reinterpreted to account for the possible redundancy of editing enzymes.

A-to-I Editing

mRNAs that encode a class of ligand-gated ion channels, the glutamate receptors and related proteins, undergo a form of editing distinct from the cytosine deamination events described above. Here, adenosine is deaminated to form inosine (fig. 1), a base not normally encountered in mRNA. Like guanine, inosine pairs preferentially with cytosine; and it interacts with ribosomes in the same way as guanine, so, in both reverse transcription and translation, edited mRNAs that have undergone an A-to-I transition appear to have exchanged an A for a G.

Glutamate receptors form heterooligomers of different subunits, encoded by the *GluR-A, -B, -C,* and *-D* genes. Receptors that contain the GluR-B protein are typically impermeable to Ca^{2+} ions. Sequence analysis has shown that the difference, in Ca^{2+} permeability, between the receptor subunits is due to a single amino acid in one of the transmembrane domains. This difference, an arginine in GluR-B where the other subunits have a glutamine, is seen at the protein and mRNA level but not in the genes that encode the different subunits. Editing of the GluR-B mRNA changes a CAG (glutamine) codon to CIG (read as CGG; arginine) at the so-called Q/R site. The GluR-B pre-mRNA sequence is predicted to form an extended stem-loop structure with pairing between the Q/R site and the downstream intronic sequence (the exon-complementary sequence [ECS]). For this reason, several groups have postulated that double-stranded (ds) RNA is the signal for editing and that a previously identified dsRNA-dependent adenosine de-

aminase (DRADA) could be the functional enzyme. Higuchi et al.(1993) showed that complementarity rather than exact sequence is, as predicted, crucial for editing the GluR-B mRNA at this site. Rueter et al. (1995) and Yang et al. (1995) have confirmed that the editing activity proceeds by adenosine deamination rather than by base excision. After the cloning of the human *Drada* (Kim et al. 1994), Dabiri et al. (1996) showed that the recombinant enzyme edits the Q/R site in vitro with no requirement for cofactors. However, purified DRADA edits substrate dsRNA promiscuously; fidelity is restored when cell or nuclear extract is added. The role of cofactors in restricting the sequence specificity of DRADA-dependent editing is analogous to the guiding function of the mooring sequence in restricting APOBEC-1 activity to a single edited site. DRADA appears to be identical to a nuclear protein that binds specifically to Z-DNA, a highly negatively supercoiled conformation of DNA that is believed to form in many transcriptionally active genes. The dsRNA-binding/-editing domain and the Z-DNA–binding domain of the molecule are distinct and can be separated by proteolysis. Herbert et al. (1995) have argued that the Z-DNA–binding domain may localize DRADA to mRNA sequences that are targeted for editing.

G-to-I editing is a general feature of mRNAs encoding glutamate receptors and related proteins. This mechanism allows for considerable versatility in glutamate-receptor function—and hence in excitatory transmission in the CNS. Like GluR-B mRNA, the homologous channel proteins, GluR6 and EAA4, are edited at the Q/R site. The latter two are also edited at two other sites, the I/V and Y/C sites, which seem to be related to the kinetic properties of the channels. Nutt and Kamboj (1994) report that they have identified five of the possible eight alternatively edited forms of the EEA4 mRNA. Editing is under developmental regulation (Paschen and Djuricic 1994), and it occurs with different levels of efficiency in the various tissues of the CNS (Sommer et al. 1991). In addition, the relative efficiencies of editing the different sites in a single mRNA species may be tissue dependent. If so, it will be of the greatest interest to learn how the substrate specificity of the editing machinery is controlled.

Other Classes of Editing

In addition to deamination of cytosine and adenosine, there is precedent for at least two other forms of mRNA editing. The Wilms tumor gene (WT1) mRNA is found in two forms with a single nucleotide difference (Sharma et al. 1994). In this case, the mRNA diverges from the gene sequence by the transition of a U to a C, suggesting that the editing activity involves enzymatic addition of an amine group to the pyrimidine base. Neonatal kidney expresses only the unedited form of the WT1 mRNA. In adult rat kidney and adult human testis tissue, however, both forms are found. The effect of this developmentally regulated editing is to convert a leucine residue to a proline, and it appears that the two forms of the WT1 protein have slightly different levels of activity as transcriptional regulators. Yet another class of editing, changing a U to an A, apparently occurs in the α-galactosidase mRNA (Novo et al. 1995). This editing step results in a transversion rather than in a transition and likely involves nucleotide excision rather than covalent modification. The change is a conservative one at the protein level (Phe to Tyr), and it is not known whether it would affect the function of the α-galactosidase protein, a lysosomal enzyme, mutations in which produce Fabry disease.

Editing in Human Disease

Although many groups have speculated that mRNA editing gone awry could cause disease, Cappione et al. (1997), in this issue of the *Journal,* make the most intriguing such claim to date. This same group previously (Skuse et al. 1996) has described C-to-U editing in the NF1 mRNA and observed that three different tumors—a neurofibroma, a neurofibrosarcoma, and an astrocytoma—taken from different patients with von Recklinghausen neurofibromatosis (associated with *NF1*) all had dramatically elevated levels of NF1 editing. In the present article, they extend this observation by quantitating the level of NF1 mRNA editing in a large number of tumors, in each case paired with constitutional tissue form the same organ of the patient; consistently, they find that tumors edit more efficiently. Furthermore, Cappione et al. show that, in general, malignant tumors, neurofibrosarcomas, edit the NF1 mRNA more efficiently than do benign neurofibromas. The authors suggest that NF1 mRNA editing plays a significant role in the disease progression in *NF1* families and that it may help explain the incidence of *NF1* gene deletions in their tumors.

The *NF1* gene is a tumor suppressor that acts through a GTPase-activating domain to suppress mitogenic signaling. NF1 mRNA editing is predicted to truncate the NF1 protein N-terminal to this domain and to abolish *NF1* tumor-suppressor function. In individuals with a constitutional NF1 mutation, loss of heterozygosity (LOH) that exposes the single mutant allele would lead to tumor formation. Biallelic inactivation as a result of LOH appears to be common among neurofibrosarcomas. However, approximately half of other malignant nerve tumors in NF1 individuals carry both alleles (Skuse et al. 1989, 1991). Furthermore, Skuse et al. (1991) found that in no case did a nonmalignant neurofibroma show LOH. This difference may suggest either

that neurofibromas and neurofibrosarcomas follow distinct paths to tumorigenesis or that LOH is a late step on a single pathway. In either case, however, it has been unclear how neurofibromas develop without LOH and why a constitutional NF1 disease allele predisposes for neurofibroma development. The observations of Cappione et al. (1997) suggest a model of tumorigenesis that may answer these questions.

NF1 mRNA editing provides a mechanism to inactivate both NF1 alleles, without LOH. If cells with only a single functional allele of NF1 have compromised growth control even without LOH, NF1 mRNA editing may reduce residual NF1 function sufficiently to trigger clonal proliferation, a first step toward neurofibroma formation. As a clone proliferates there will be a selective growth advantage for any further increase in editing, since this will reduce NF1 function still further. LOH may represent the end stage of this progression, in which NF1 function is eliminated completely, perhaps inducing the tumor to become malignant. This model appears to explain the occurrence of neurofibromas without LOH, but it raises the question of whether LOH continues to confer a growth advantage on cells with high levels of NF1 mRNA editing. A prediction of the model is that those malignant sarcomas that carry both NF1 alleles should have particularly high levels of mRNA editing.

Other mechanisms could account for the observed increase in NF1 editing in tumors. As a trivial explanation, increased editing activity might correlate with tumorigenesis but play no role in cellular growth. A more interesting possibility is that NF1 mRNA is not the only target of editing in neurofibromas or neurofibrosarcomas. In this case, it might be easier to understand the growth advantage of LOH in a cell population that already has high levels of editing activity.

Animal Models for mRNA Editing–Related Diseases

If one accepts the claim of Cappione et al. that von Recklinghausen neurofibromatosis is in part a disease of mRNA editing, the prospects of developing a model of disease progression by using rodents suddenly seem more distant. Rodents do edit mRNA, and they also express NF1, but, by a quirk of molecular evolution, the homologous site in rat NF1 mRNA has a highly divergent mooring sequence that does not support editing (Skuse et al. 1996). Hence, heterozygous rats, unlike NF1 carriers in humans, may not be at great risk of spontaneous neurofibromas or fibrosarcomas. However, the data on mRNA-editing levels in these tumors suggest a parallel to the tumor-prone APOBEC-1 transgenic animals. It would be interesting to learn whether NF1-related tumors, like cells that overexpress APOBEC-1, edit their mRNAs promiscuously. Is so, these apparently dissimilar genetic backgrounds could promote tumorigenesis by a related means—namely, by effects of editing other mRNAs that are related to growth control. As more is learned about the mechanisms and specificity of mRNA-editing pathways, such unexpected parallels may become commonplace, and some now-puzzling differences in the progression of diseases in different animals may become clear.

Note added in proof.—Melcher et al. (1996) recently identified Red2, a novel DRADA homologue that is expressed in a distinctive pattern in various tissues of the CNS. Differences in target-sequence specificity among the three known members of the DRADA family of enzymes may help explain the complex regulation of A-to-I editing in the brain.

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